lower limit to 0.6 μm, the upper limit for the median size of a nanoparticle population (See Claim 7, also page 5, 4th paragraph).

Rejections of Claims 1-4, 6 and 15-18 under 35 U.S.C. 102(b) as being anticipated by Moore *et al.* (Section 13 of the Office Action).

This rejection is traversed for the reasons that follow.

Moore discloses that the intraperitoneal immunization with HIV gp120 antigen favors the induction of T_H1 cells when the antigen is entrapped in PLG-"microparticles" having a mean diameter in the range 0.368 to 0.501 μm. For purposes of the present application, such a population is a nanoparticle population. Moore does not provide information as to actual or expected response with microparticles.

Rejections of Claims 1-4, 6 and 15-18 under 35 U.S.C. 102(b) as being anticipated by Nixon *et al.* as evidenced by Garcon et al. or Rook et al. (Section 14 of the Office Action)

This rejection is traversed for the reasons that follow.

The Nixon reference not only does not disclose the present invention but also teaches away from the present invention.

Nixon studied three different sizes of particles containing CS peptide for CTL response.1) < 500 nm, 2) 2 μm, and 3) > 7 μm. Nixon teaches that the first group containing < 500 nm sized particles (nanoparticles according to Applicant) was the more efficient inducer of CTL (i.e., a T_H1 response) than larger particles (See page

1527, second paragraph and Figure 4, page 1528). To that extent, Nixon is consistent with Moore, discussed above.

In contrast to Moore, however, Nixon also has data on microparticles (the 2 μm population), as defined by Applicant. Nixon discloses that the microparticle population is less effective than the nanoparticle population at inducing a T_H1 response. Therefore, Nixon would not lead one to expect that, for microparticles, there would be a T_H1-polarized response. If anything, Nixon teaches away from such a polarized response,

The disclosures of Garcon and Rook do not contradict Applicant's position as regards Nixon. Rook et al. used neither microparticles nor nanoparticles. Garcon used emulsions rather than microparticles or nanoparticles.

Rejections of Claims 1, 5, 15, and 19 under 35 U.S.C. 103(a) over Moore *et al.* in view of Locht *et al.* (Section 15 of the Office Action).

This rejection is traversed for the reasons that follow.

As noted above, Moore's data is derived from nanoparticle populations rather than microparticle populations. Locht is cited by the Examiner as teaching the production of pertussis FHA antigen. As a result, Moore and Locht in combination do not make Applicant's claimed inventions obvious.

Rejections of Claims 1, 5, 15, and 19 under 35 U.S.C. 103(a) over Nixon *et al.* as evidenced by Rook et al., and in view of Jones *et al.* (1997) and Mills *et al.* (Section 16 of the Office Action).

This rejection is traversed for the reasons that follow.

As noted above, Nixon does not lead one to expect a T_H1-polarized response using microparticles. Indeed, Nixon tends to teach away from such a result.

Jones et al. (1997) does not have any T_H2 data. Also they do not disclose the size of their particles.

Mills et al. used neither microparticles nor nanoparticles.

Rook et al. used neither microparticles nor nanoparticles.

Rejections of Claims 1-6 and 15-19 under 35 U.S.C. 103(a) over Jones *et al.* (1995) in view of Nixon *et al.* and Tice *et al.* or O' Hagan (Section 17 of the Office Action).

This rejection is traversed for the reasons that follow.

As noted above, Nixon's disclosure tends to teach away from using microparticles to induce a T_H1 polarized response.

Jones (1995) used particles with a mean diameter of 24 μm, larger than that of Applicant's microparticles.

Tice *et al.* discloses using an encapsulated antigen in the form of microparticles sized 1-10 μm to elicit a humoral (T_H2) immune response. (e.g. column 15, lines 11-43). On the contrary, the Applicant discloses a T_H1-polarized response for microparticles.

O'Hagan has no data on TH1 vs TH2 immunity. Additionally, he does not make a distinction between microparticles and nanoparticles as understood in the present application.

Rejections of Claims 15 and 20 under 35 U.S.C. 103(a) over Nixon *et al.* as evidenced by Rook and in view of Jones *et al.* (1996) (Section 18 of the Office Action)

This rejection is traversed for the reasons that follow.

The reasons that Nixon and Rook, either alone or in combination, would not make Applicant's inventions obvious have been discussed above. Jones et al. (1996) used particles with a mean diameter of 7.35 μm (page 33, section 6.1) larger than what Applicant defines as the median size of a microparticle. Furthermore, Jones does not disclose T_H1 and T_H2 data needed to determine whether there is a TH1-polarized response.

In view of the foregoing remarks, it is respectfully submitted that all of the claims now remaining in this application are allowable and such favorable action is respectfully requested.

Respectfully submitted,

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September 17, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of inducing a T_H1 polarized immune response to an antigen, comprising parenterally administering to a subject microparticles sized such that at least 50% of the microparticles are at least 0.6 μm and a least 50% of the microparticles are less than 5 μm, the microparticles comprising the antigen entrapped or encapsulated by a biodegradable polymer.

15. (Amended) A vaccine formulation for enhancing the T_H1 immune response to at least one antigen and adapted for parenteral administration comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of microparticles sized such that at least 50% of the microparticles are at least 0.6 μm and at least 50% of the microparticles are less than 5 μm, the microparticles comprising the at least one antigen entrapped or encapsulated by a biodegradable polymer.

CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment Under 37 CFR 1.116, a Petition for Extension of Time, A Fee Transmittal for FY2002, and a Transmittal Form, re Application Serial No. 09/386,266 are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231 on this 17TH day of September, 2002.

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